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| CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110 | | | EXAMINER CRANE, LAWRENCE E | |
| | | | ART UNIT 1623 | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary

Application No.

10/598,535

Applicant(s)

HERDEWIJN ET AL.

Examiner

Lawrence E. Crane

Art Unit

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on April 5, 2010 (amendment).
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-29 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 14-29 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 01 September 2006 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 04/05/2010
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. Examiner notes with appreciation the amended descriptions. However, the Figures include numerous indicia of process steps ("a," "b," ... "h," but said steps have not been defined in the Figures or in the Brief Descriptions of the Drawings. Applicant is respectfully requested to make the Figures complete by adding descriptions of the process steps. This is a second request.

Claims **1-13** were previously cancelled, no claims have been newly cancelled, claims **14-19, 21-23 and 25** have been amended, the title has been amended, the disclosure had already been amended at page 1 and has been newly amended at several locations, the Abstract has been amended as requested, and new claims **27-29** have been added as per the amendment filed April 5, 2010. One additional or supplemental Information Disclosure Statement (1 IDS) filed April 5, 2010 has been received with one cited non-US patent reference and made of record.

Claims **14-29** remain in the case.

Note to applicant: when a rejection refers to a claim **X** at line **y**, the line number "**y**" is determined from the claim as previously submitted by applicant in the most recent response including ~~lines deleted by line through~~.

35 U.S.C. §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

In claims **20 and 26** the definitions of the variable "**V**" as "silyl" must be read to include structural alternatives wherein Si-H bonds are present, thereby rendering the compounds being claimed pyrophoric (spontaneously flammable in air). As a consequence a substantial portion of the compounds being claimed appear to lack reasonable utility for the purpose intended in view of their excessive oxygen sensitivity.

Applicant's arguments filed April 5, 2010 have been fully considered but they are not persuasive.

Applicant argues that the noted term is appropriate because the only exemplifications provided in the disclosure are exclusively tri-substituted silyl moieties. Examiner notes the argument but also notes that applicant's argument in effect required a re-definition of the term "silyl" that is inconsistent with the known in the art definition thereof. Examiner alternatively respectfully suggests that applicant may elect to introduce by amendment the specific silyl groups listed in the disclosure, or if possible (not new matter), the term -- trisubstituted silyl -- including substituent definitions into the noted claims.

Claims **14-20 and 22-29** are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabled for the synthesis of a small number of nucleoside and nucleotide analogues wherein linker-attached 3-phosphonyl-L-threofuranosyl moieties have replaced ribo- or 2'-deoxyribofuranosyl substituents, for the synthesis thereof, for the pharmaceutical compositions thereof, and for the treatment of HIV therewith, does not reasonably provide enablement for the synthesis, or the effective non-HIV anti-retroviral administration of nearly all of the vast array of compounds claimed herein optionally in the presence of "a retroviral enzyme inhibitor," wherein determination of the scope of the claimed subject matter is further complicated by the presence of indefinite terms including "derivatives," and several substituent definitions that fail to completely define the substituent structures in question because of the presence of functional terminology: e.g. the term "Phos" in claim **20**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988)) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims is found to be excessive because the definitions of structural variables, and the definition of diseases claimed to be effectively treated, are much more comprehensive and broad in scope than the small number of specific embodiments provided herein.

B. The nature of the invention: The instant claims are directed to L-threofuranosyl nucleosides and 3'-(substituted)-phosphonate substituted nucleotide analogues thereof, the syntheses thereof, intermediates necessary for the executions of said syntheses, pharmaceutical compositions thereof, and methods of treating viral infections therewith including at least one retroviral infection (HIV) by the administration of an effective amount of one of said nucleotide analogues to a host in need thereof.

C. The state of the prior art: The prior art of record herein presently includes disclosures of both erythro- and threo-furanosyl nucleosides and nucleotides and analogues thereof, and also disclosures of some medicinal activity thereof.

D. The level of one of ordinary skill would be expected to include knowledge of the organic synthesis of nucleosides, nucleotides and analogues thereof, and the medicinal testing of said compounds *in vitro*.

E. The level of predictability in the art: The relatively small quantity of prior art presently of record the is directly relevant to the instant claimed compounds and to the syntheses thereof supports the view that the instant art area is not well explored at present and therefore likely to be unpredictable, particularly in the area of medicinal activity.

F. The amount of direction provided by the inventor: The instant disclosure enables the synthesis of a very small number of L-threofuranosyl nucleoside and nucleotide derivatives, and also enabled the administration of two of these products to the treatment of HIV.

G. The existence of working examples: This subject is dealt with in previous paragraphs.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is found to be excessive because the instant disclosure does not provide a sufficient comprehensive disclosure to adequately enable such broadly and indefinitely drafted claims as noted in the amended analysis provided above.

Applicant's arguments with respect to claims **14-26** have been considered but are moot in view of the new grounds of rejection. This new ground of rejection was necessitated by applicant's amendments.

The disclosure is objected to because of the following informalities:

The term “natural or non-natural nucleobase” occurs repeatedly in the disclosure. But the particular species associated with the terms “natural” and “non-natural” as terms defining the term “nucleobase” are not clearly identified as such in the disclosure, making it impossible to know the definitions implied by the two parts of the initially cited term. Clarification of the disclosure definitions of “natural nucleobase” and “non-natural nucleobase” is respectfully requested.

Appropriate correction is required.

Claim 21 is objected to because of the following informalities:

In claim 21, last line, the term “an stereoisomer” is grammatically incorrect.

Appropriate correction is required.

Claims 14-29 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 14 at line 15, the term “oxygen” and “sulfur” refer to elements. Did applicant intend the terms to read -- -O- -- and -- -S- --, respectively?

Applicant’s arguments filed April 5, 2010 have been fully considered but they are not persuasive.

Examiner notes that applicant has identified the X variables as “an atom,” wherein, in fact the variables represent -- a divalent substituent moiety selected from the group consisting of -O- and -S- -. Appropriate amendment is respectfully suggested. Taken alone examiner agrees that O and S are elements, but applicant is herein defining a compound wherein the noted elements have been incorporated into the generic structures as divalent substituent moieties.

Applicant's arguments with respect to claims **14-26** have been considered but are moot in view of the new grounds of rejection. This new ground of rejection was necessitated by applicant's amendments.

In claim **14** at line 19, the terms "heterocyclic" and "heterocyclic-alkyl" are incompletely defined because the identities, the ring size(s), the degree(s) and the location(s) of unsaturation(s), and the location(s) of the hetero atom(s) have not been specified in the claim. See also claim **28** wherein a similar error occurs.

Applicant's arguments filed April 5, 2010 have been fully considered but they are not persuasive.

Applicant has cited the disclosure definitions present at pages 12-14 as providing proper definitions that can be relied on as definitions of the noted terms. Examiner respectfully disagrees, noting that the first said definition at page 12, line 14, includes a violation of 35 U.S.C. § 112, second paragraph, because of the presence of the term "including," open language that permits additional subject matter not provided by the disclosure. For this reason the above rejection has been maintained.

In claim **14** at lines 17 and 29 a Markush preamble is provided, but at lines 23 and 30 there is no -- and -- between the last two Markush group members. Appropriate addition of the term -- and -- is respectfully requested.

Applicant's arguments filed April 5, 2010 have been fully considered but they are not persuasive.

The above noted rejection is maintained because the Markush group now located between lines 17 and 25 continues to be no -- and -- term between the last two Markush group members. See also claim **14** at line 38 wherein the term -- and -- is also missing in another Markush group.

In claim **14** at lines 43-44, the definition provided is unclear. Applicant is respectfully requested to amend to make the meaning unequivocal.

Applicant's arguments filed April 5, 2010 have been fully considered but they are not persuasive.

Examiner notes the addition of punctuation, but continues to find the combination of X⁴ and R¹, or X⁵ and R², to imply structures that require far too much speculation to completely define given the present guidance provide by the noted claim language.

In claim 14 at line 61-62, the term “solvates” is directed to subject mater that has not been adequately defined within the claim and therefore said term renders the claim incomplete. See also claim 15-16, 21 (“solvates and pro-drugs”) and 28 for the same error.

Applicant’s arguments filed April 5, 2010 have been fully considered but they are not persuasive.

As applicant has noted, the term “solvates” has been defined at page 15 at lines 15-20 of the disclosure. However, said definition does not meet the requirements of 35 U.S.C. §112, second paragraph because the particular “solvate(s)” being claimed herein cannot be determined with adequate particularity following reference to this part or any other part of the disclosure. Examiner respectfully suggests deletion of the noted term. For this reason the instant rejection has been maintained.

In claim 17 at lines 2-3, the Markush group is incomplete because the term -- and -- is missing from between the last two Markush group members (the term introduced by amendment at line 3 should read -- and 2,6-diaminopuriny --), an error that implies a major carbon valence error. See also claims 18 and 19 at line 3 wherein the same error reoccurs.

Applicant’s arguments with respect to claims 14-26 have been considered but are moot in view of the new grounds of rejection. This new ground of rejection was necessitated by applicant’s amendments.

In claim 20 at line 22, the term “Phos” is incompletely defined by the terms at the end of the noted line because the complete structures of the named functional groups cannot be entirely determined from the terms provided.

Applicant’s arguments filed April 5, 2010 have been fully considered but they are not persuasive.

Applicant notes the above rejection, but does not make an argument directed specifically to respond to the instant rejection. Therefore, the above rejection has been repeated. Examiner

notes that the complete structure of the group has not been defined with a formula, and that the included terms "O-protected," "alkoxy" and "alkyl" have not been defined as to groups and specific location(s), therefore rendering the metes and bounds of the noted claim indefinite.

In claim **29** the term "adenine and thymine" is directed to two separate compound, not to two substituents. Examiner respectfully suggests amendment of the noted term to read -- 9- adeninyl and 1-thyminyl --.

Applicant's arguments with respect to claims **14-26** have been considered but are moot in view of the new grounds of rejection. This new ground of rejection was necessitated by applicant's amendments.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

"A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

(c) the invention was described in

(1) an application for patent described under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application filed under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a)."

(f) he did not himself invent the subject matter sought to be patented."

Claim **26** is rejected under 35 U.S.C. §102(b) as being anticipated by **Dujardin et al.** (PTO-1449 ref. **AR**).

Applicant is referred to the cited reference at page 1557 wherein compounds **8g**, **8h**, **9g** and **9h** each anticipate the structure at line 3 of claim **26** (first structure provided).

Applicant's arguments filed April 5, 2010 have been fully considered but they are not persuasive.

Applicant argues that the acyl group in the above cited art is not included within the definition of "acyl" provided by applicant, and therefore that the instant defined term "acyl" is properly included in the above noted claim. Examiner respectfully disagrees, noting that at least two chemical dictionaries define the term "acyl" as being "the radical produced by removal of an OH group from the carboxyl of a carboxylic acid," and do not mention any further limitations *in re* variations of the chemical structure of the R group of "O=C-R," the generic formula for all acyl radicals. For this reason the above rejection has been found to remain valid. Examiner respectfully suggests that applicant may elect to include by amendment a -- proviso -- that excludes the subgenus of the prior art α -ketoacyl groups.

Claims **14-25 and 27-29** would be allowable if rewritten or amended to overcome the rejections under 35 U.S.C. §112 and §101 set forth in this Office action.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. S. Anna Jiang, can be reached at **571-272-0627**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status Information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see < <http://pair-direct.uspto.gov> >. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

LECrane:lec
08/06/2010

/Lawrence E. Crane/

Primary Examiner, Art Unit 1623

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